DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
National Cancer Institute
Bethesda, Maryland 20892

October 23, 1997

Larry G. Hart M.D.
11 Alexander Drive
Building 101
Research Triangle Park, NC 27709

Dear Dr. Hart:

This letter is in reference to the possible listing of tamoxifen for the 9th Report on Carcinogens. As I will not be able to attend the public meeting on October 30-31, I would like to share with the Committee my experience with this drug.

Tamoxifen is the most widely used drug in the country for the treatment of breast cancer. It has been demonstrated in rigorously conducted randomized clinical trials to increase survival in all stages of breast cancer. It also reduces the risk of developing a new breast cancer in the opposite breast in women who already have the disease. It is for this reason that it is being studied in the primary prevention of breast cancer in women who are at increased risk for the disease. In the Breast Cancer Prevention Trial (BCPT) over 13,300 women have been randomized to receive tamoxifen or a placebo for five years. Although the original plan was to accrue 16,000 women the sample size was decreased due to the extraordinary high risk of the participants.

The most definitive data on the role of tamoxifen in endometrial cancer will come from the BCPT. Since mid 1994 women entering the study who have an intact uterus were required to have an endometrial biopsy indicating no signs of hyperplasia or other pathology prior to being randomized to tamoxifen or placebo. Follow-up on this group of over 1000 women with no pre-existing uterine conditions should inform us greatly about the possible role of tamoxifen in the development of endometrial cancer. Results of this clinical trial should be available within two years.

In October, 1995 I wrote to the Office of Environmental Health Hazard Assessment in California regarding the listing of tamoxifen as a carcinogen. I have enclosed a copy of that letter because I feel that the information in it is critical to any discussion of this topic. As the data from ongoing studies matures, it appears to show that the association of tamoxifen and endometrial cancer is affected by prior exposure to estrogen replacement therapy and other known risk factors (e.g.obesity). The case-control study conducted by Dr. Leslie Bernstein at University of Southern California is now completed. The results (which you should receive directly from Dr. Bernstein) continue to support the preliminary findings described in that letter. Since this is the only study that includes detailed data regarding prior exposures, which are known risk factors for development of endometrial cancer, I would urge you to consider it carefully.

I hope the Committee will consider this information in their deliberations regarding the carcinogenic potential of tamoxifen.

Sincerely,

Leslie G. Ford

Leslie G. Ford M.D.
Associate Director
Early Detection and Community
Oncology Program
Division of Cancer Prevention

Enclosure

cc: Dr. C.W. Jameson

DEPARTMENT OF HEAL. & HUMAN SERVICES Public Health Service

National Institutes of Health
National Cancer Institute
Bethesda, Maryland 20892

October 30, 1995

Ms. Catherine Caraway
Office of Environmental Health
Hazard Assessment
601 N. 7th Street
MS:241, P.O. Box 942732
Sacramento, California 94234-7320

Dear Ms. Caraway:

This letter is a response to a recent request from Dr. Richard Becker for information on tamoxifen. I am happy to provide some additional information about tamoxifen for your consideration pursuant to the Office of Environmental Health Hazard Assessment's (OEHHA) review of data for rendering an opinion as to whether this agent has been clearly shown to cause cancer.

In my June letter to Dr. James Stratton, I indicated that there was no evidence of tamoxifen-associated hepatocellular carcinoma in humans, and that it is premature to make a definitive determination as to whether tamoxifen plays a causal role in the development of endometrial cancer. Those conclusions still apply.

Although there are several reports that indicate an association between endometrial cancer and tamoxifen exposure with a relative risk on the order of 2 to 3, there are study design issues that mitigate interpretation of the observed relative risks. Two of these are detection bias and confounding related to prior exposures such as the use of exogenous estrogens, which have been linked to the development of endometrial cancer.

Up to now, studies have not taken into consideration whether endometrial cancers are more frequently detected in tamoxifen users because more biopsies are done in this group of women. Use of tamoxifen may unmask the existence of a prior lesion by causing it to be symptomatic, or women with symptoms who have also used estrogen or tamoxifen may be more likely to seek an evaluation of their symptoms. The issue of whether tamoxifen administration or its history may lead to the detection of previously existing prevalent cases of endometrial cancer

is unresolved. Also, epidemiologic evidence indicates that factors other than tamoxifen exposure must be considered when interpreting the results of endometrial cancer studies. These issues must be resolved before any absolute conclusion can be reached regarding the carcinogenicity of tamoxifen.

Ongoing research supported by the National Cancer Institute is attempting to answer questions about the impact of pre-existing endometrial lesions and prior exposure to exogenous estrogens on women who use tamoxifen. Two studies are of particular importance in answering these questions. Preliminary results are available for one of these studies, which involves an in-depth analysis of prior hormone exposure in tamoxifen users.

The information that I am sharing with you is preliminary and comes from a case control study being conducted by Dr. Leslie Bernstein at the University of Southern California School of Public Health. This is the first endometrial cancer study that obtains a detailed history of exposure to hormones (oral contraceptives, estrogen replacement therapy and hormone replacement therapy) as well as tamoxifen use in breast cancer patients. It is a case control study that has started with cases from the Los Angeles SEER area. To reach the planned study size of approximately 1,000, cases will be added from three additional registries: Seattle, Atlanta and Iowa. The cases are breast cancer patients who have developed a subsequent endometrial cancer. The control women are breast cancer patients without endometrial cancer, who are matched 2 to 1 with case patients.

The preliminary and confidential information that is available from Dr. Bernstein's study at this time is provided by 168 cases and 290 controls from Los Angeles. Based on these 458 women, the preliminary estimate for relative risk of endometrial cancer after using tamoxifen without a prior history of hormone use compared to individuals who have used neither tamoxifen nor hormones is 1.19. This value is not significantly different from one, i.e. consistent with no effect. For this preliminary data set, when a patient has used both tamoxifen and hormones, only then does the estimate of her relative risk reach about 2.67 and achieve statistical significance. Although this study is not complete, it appears that the risk of endometrial cancer associated with tamoxifen use is not higher than previously thought (less than or equal to 3.0). Much of the risk may be due to prior exposure to hormones, a fact not previously recognized. Based on the result from this study so far, it appears that the risk of tamoxifen-associated endometrial cancer is low. The completion of this study will see the addition of patients from the three other SEER registries mentioned above, enhancing the statistical power of the study as well as the generalizability of the results.

A second NCI-sponsored study that will clarify the controversy surrounding endometrial cancer in tamoxifen users is the Breast Cancer Prevention Trial (BCPT). This is a randomized, placebo-controlled study of 16,000 women who are at increased risk of developing breast cancer based on known risk factors. The intervention arm of the BCPT involves taking tamoxifen at a dose of 20 mg a day for five years. Since October 1994, women with an intact uterus, who choose to enter the study, must have an endometrial biopsy prior to randomization. Approximately 500 women to date have had an endometrial biopsy as part of the entry evaluation, and all subsequent participants with a uterus will have a baseline endometrial sampling, potentially leading to group of 3,000 such women. This approach will help to resolve the confusion about detection bias, since potential participants with pre-existing endometrial abnormalities are screened out of participating in the BCPT. Thus for the group of women randomized after October 1994, we will have a prospective double blind placebo controlled study of the effect of tamoxifen on the endometrium.

Additional information about risk of endometrial cancer in women who have received tamoxifen is also provided by a recently published nested case-control study. A copy of this article by Dr. Linda Cook and co-authors is attached for your review. Briefly, the results indicate that exposure to tamoxifen for up to two years, is associated with a subsequent relative risk of endometrial cancer on the order of 0.6 (again, not significantly different from 1.0 and therefore consistent with no effect). Consequently, in this study group consisting of women developing ovarian, endometrial or breast cancer after a preceding diagnosis of breast cancer, there was no evidence of an increased risk of subsequent endometrial cancer. This information may be especially meaningful, when considered in the context of data from the Stockholm Study, where the majority of so-called tamoxifen-associated endometrial cancers occurred after an exposure to tamoxifen of two years or less. This result is highlighted in Figure 2 of the article by Jordan and Morrow that you will find enclosed with this letter.

Finally, I do feel that there are problems with the analysis and interpretation of studies discussed in the draft document, *Evidence on the Carcinogenicity of Tamoxifen*. Although the discussion goes to great length to examine reasons about why increased risk was not detected, there was a noticeable neglect of critical assessment as to why the results of various studies may have over estimated risk. As discussed above, issues concerning bias and confounding with respect to the study of endometrial cancer in women taking tamoxifen have not been resolved. A further example of a possibly unbalanced presentation in the draft document appears to occur when one paper is cited as supporting the hypothesis that tamoxifen

causes endometrial abnormalities, but a paper by the same author a year later is not considered even though the conclusion as stated in the title is, *Continuous Tamoxifen Treatment in Asymptomatic, Postmenopausal Breast Cancer Patients Does Not Cause Aggravation of Endometrial Pathologies*. A copy of the latter paper is also enclosed.

Please let me know if you have additional questions for me. I hope the information in this letter will be useful in your assessment of tamoxifen.

Sincerely,

Leslie G. Ford

Leslie G. Ford, M.D.
Chief, Community Oncology and Rehabilitation Branch
Division of Cancer Prevention and Control

Enclosures (3)